Single Molecule Biophysics and Biology of Cellular Identity

Grant Award Details

Single Molecule Biophysics and Biology of Cellular Identity

Grant Type: Research Leadership

Grant Number: LA1-08013

Project Objective: To support pioneers in the stem cell field who move their labs to California. Dr. Darzacq moved his group to UC Berkeley from France with this award. His group has focused its activity on three 3 goals: establishing new technologies for imaging molecular processes in differentiating tissues, studying the cellular reprograming of the pre-initiation complex concomitant to differentiation events during tissue regeneration and establishing a research program to study genome architecture and the proteins establishing it during differentiation in ES cells.

Investigator:

Name:	Xavier Darzacq
Institution:	University of California, Berkeley
Type:	PI

Disease Focus: Other

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $4,247,155

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Grant Application Details

Application Title: Single Molecule Biophysics and Biology of Cellular Identity

Public Abstract:

One of your earliest childhood biology lessons probably occurred when your body demonstrated to you that your skin is an organ that is able to self-regenerate. Indeed wound healing is a fascinating process in which cells carry out a precise and complex choreography that includes cellular differentiation and regulation of gene expression.

Our lab studies a particular cell type called dermal fibroblasts. If a wound occurs, they migrate to the site of injury, change into muscle like cells (myofibroblasts) that contract to help with wound closure, and, once the wound has healed, enter programed cell death to clear the work area. Disruption to this process can result in chronic ulcers or keloid scarring. A major goal of our studies is to understand how the fibroblast to myofibroblast transition is regulated, so that therapeutic strategies can be devised to prevent and treat this pervasive problem.

In addition to our motivation to understand wound healing in order to learn how to control it and cure its pathologies, wound healing is an accessible system to study more general differentiation events involved in tissue regeneration. By studying the changes that fibroblasts undergo during wound healing, we revealed an important mechanism of gene regulation that could help to explain more generally how cells maintain a particular identity and how they can be driven to a different state. The molecules we identified are known to control general gene activity as well as the spatial organization of genes within the cell's nucleus. The studies proposed here will further investigate those findings.

One of the ways in which our laboratory studies how cells control gene activity is by directly visualizing gene expression. Using highly specialized microscopy, biochemistry and computer analyses, we are able to observe the behavior of individual gene regulatory molecules within individual living cells. We will continue to use and improve these methods to better understand how genes are controlled. We believe that these studies will open the door to new strategies in cellular reprogramming and potentially to new strategies for modifying cells for therapeutic use.

Statement of Benefit to California:

Our research program includes clinically relevant and translational studies of wound healing, development and transfer of new imaging technologies to enable investigators to visualize the behavior of individual molecules within living cells, and basic biological studies seeking to understand fundamental mechanisms of gene regulation that control stem cell pluripotency and differentiation. These endeavors will benefit the State of California in various different and overlapping ways.

Successful development of stem cell-based therapies hinges on the ability to control cell identity and cell fate. By contributing to the understanding of fundamental gene regulatory mechanisms controlling pluripotency and tissue-specific differentiation, the research proposed here has the potential to influence and positively impact a wide range of regenerative medicine studies ongoing in the state.

Chronic skin ulcers are a pervasive and dangerous human medical problem. Current treatments can be slow and painful, and are too often ineffective, resulting in the necessity of limb amputation. The true economic and personal cost of chronic ulcers is difficult to quantify because public health research most frequently includes it as a symptom of systemic disease. However, in 2009 chronic ulcers were estimated to affect 6.5 million patients in the Unites States, with treatment costs in excess of 25 billion dollars. Our identification of specific factors that control the fibroblast to myofibroblast transition suggests new approaches to differential diagnosis and to treatment of chronic wounds using fibroblasts and myofibroblasts as direct targets or therapeutic agents.

The ability to detect, track and manipulate individual gene regulatory molecules in living human cells is a disruptive technology that already is having a major impact in developmental biology and stem cell research. Technologies for imaging individual molecules in live cells are evolving so rapidly that they are difficult to commercialize and are therefore available only to a relatively small number of laboratories that are able to build these systems from component parts. Our lab will serve as a center to help develop these technologies, and to help other laboratories adopt these powerful new research tools. California also has a rich industrial base in microscopy development and engineering. The development and implementation of new super resolution live cell imaging technologies such as we propose here will offer many opportunities for collaboration between industry and academia, opening new markets and enabling the spread of these innovations throughout academic and bio-pharmaceutical laboratories. This synergism, in turn, will accelerate research in regenerative therapeutics.
